ABSTRACT OF THE DISCLOSURE

A total synthesis of elenolic acid, Formula XIV (R and R₂ are hydrogen, R₁ and R₃ are methyl) and the analogs thereof, of Formula XIV:

wherein R and R₃ are alkyl of 1 to 8 carbon atoms, inclusive, wherein R₁ is alkyl of 1 to 4 carbon atoms, inclusive, and wherein R₂ is selected from the group consisting of hydrogen and alkyl of 1 to 4 carbon atoms, inclusive, is carried out by a multi-step process starting from cyclopentadiene. Compounds of Formula XIV have virucidal and hypotensive activity and can be used as hypotensive agents in mammals (U.S. Pat. 3,033,877) or as virucidal agents to decontaminate surgical instruments, hospital walls, swimming pools, or can be used for nasal washes in mammals.

BACKGROUND OF THE INVENTION

(1) Field of the invention

The present invention is concerned with a process for the synthesis of elenolic acid, analogs and derivatives thereof and with the intermediates in said process.

(2) Description of the prior art

Already in 1931 A. D. Burnett and M. Oliviero (Bull. Acc. Med. 122, 191 (1932)) recognized that an extract from the leaves of the olive tree (Olea Europaea) contained a hypotensive principle (see also L. Panizzi et al., Gazz. Chim. Ital. 90, 1449 (1960)).

W. L. Constantijn Veer, U.S. Pat. 3,033,877, issued May 8, 1962, described the preparation of elenolic acid, salts, "ether-esters" and other analogs of elenolic acid. The only method for the preparation of this acid, salts or derivatives thereof was by extraction and chemical treatment of the extracts of the leaves or the fruit of Olea Europaea. In particular the aqueous press juice resulting from pressing the ripe fruit was used. The amount of acid obtained was always exceedingly small; e.g., U.S. Pat. 3,033,877 reports that from 250 kg. of leaves of Olea Europaea 114 g. of an impure oil was obtained concerning which it was stated "consists for the greater part of elenolic acid." The same patent reports that from 160 liters of press juice 0.35 g. of elenolide (lactone form of elenolic acid) was obtained.

The Upjohn Company from a batch of 37,000 liters of olive press juice (obtained in Spain) isolated 1,300
3,703,530

ester (II); reacting II at low temperatures with an alkylmaleic anhydride (B) to obtain the corresponding 2,3-dicarboxy-5-norbornene-7-acetic acid alkyl ester 2,3-anhydride (III); hydrolizing III to obtain the corresponding 2,3-dicarboxy-5-norbornene-7-acetic acid alkyl ester (IV); treating IV with oxime tetroxide, or with a chlorate salt and a catalytic amount of oxime tetroxide, to obtain the corresponding 2,3-dicarboxy-5,6-dihydroxynorbornene-7-acetic acid alkyl ester (V); treating V with an aldehyde or ketone, preferably acetoacetic acid, to obtain the corresponding 2,3-dicarboxy-5,6-dihydroxynorbornene-7-acetic acid, alkyl ester, acetal or ketal (VI); subjecting VI to electrolysis in a water-pyridine solution containing 1 to 5% of a tertiary amine such as triethylamine to obtain the corresponding 5,6-dihydroxy-2-norbornene-7-acetic acid, alkyl ester acetal or ketal (VII); oxidizing VII with aqueous potassium permanganate and sodium periodate to give the corresponding 2-alkanoyl-3,4-dihydroxy-5-carboxycyclopentanecetic acid, alkyl ester, acetal or ketal (VIII); esterifying (VIII) with an alkanol in the presence of a dehydrating agent such as a carboxylic anhydride or with diazoalkane in the corresponding 2-alkanoyl-3,4-dihydroxy-5-carboxycyclopentanecetic acid, 1,5-dialkyl ester, acetal or ketal (IX) (the two alkyl groups 1 and 5 can be alike or different); reducing IX with an alkali metal borohydride to give the corresponding 2-(1-hydroxyalkyl) - 3,4-dihydroxy-5-carboxycyclopentanecetic acid, 1,5-dialkyl ester, acetal or ketal (X); converting X to a 2-ester, e.g., the methanesulfonate of 2-(1-hydroxyalkyl) - 3,4-dihydroxy-5-carboxycyclopentanecetic acid, 1,5-dialkyl ester, acetal or ketal (XI); treating XI with a dilute aqueous acid to give 2-(1-hydroxyalkyl)-3,4-dihydroxy-5-carboxycyclopentanecetic acid, 1,5-dialkyl ester, 2-ester, e.g., 2-methanesulfonate (XII); oxidizing the glycol XII with aqueous periodate salt to give the corresponding 2-hydroxy-3-(1-hydroxyalkyl) - 5-carboxy - 3,4-dihydro-2H-pyran-4-acetic acid, 4,5-dialkyl ester, 3-ester (XIII); heating compound XIII in a basic medium, pH 7.2 to 9, to give the corresponding compound (XIV), e.g., methyl eledonate when R, R₃ and R₄ are methyl and R₁ is hydrogen. Compound XIV can be selectively hydrolized with dilute mineral acid to an acid of Formula XV. If in Formula XV R₁ and R₂ are methyl and R₃ is hydrogen, the acid is eledonic acid. Alternatively, compound X can be hydrolized with dilute aqueous acid to give compound XII where X₃ is hydroxy.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The alkyl groups herein used having from 1 to 4 carbon atoms, inclusive, such as R₃ and R₄ are illustratively methyl, ethyl, propyl, butyl, isobutyl, secondary butyl and the like.

The alkyl groups herein used having from 1 to 8 carbon atoms, inclusive, comprise the group of alkyl groups above with up to 4 carbon atoms, and pentyl, hexyl, heptyl, and octyl and the branched isomers thereof.

The parameter X₁ herein used is a negative element or group which is reactive in metallic reactions with compounds containing a strong positive element such as sodium, potassium or lithium. Such negative elements or groups are illustratively iodine, bromine, methanesulfonate, butanesulfonate, benzenesulfonate, toluenesulfonate and the like.

The parameter X₂ is an alkylating agent of the formula

\[ R \quad X₁ \quad CH₂ \quad COOR(A) \]

wherein R, R₂, and X₁ are as given above, to give the corresponding 1,3-cyclopentadienyl lithium, sodium, or potassium (I) with an alkylating agent of the formula

\[ R \quad CH₂ \quad COOR(A) \]

wherein R, R₂, and X₁ are as given above, to give the corresponding 1,3-cyclopentadienyl-5-acetic acid alkyl ester (II); reacting II at low temperatures with an alkylmaleic anhydride (B) to obtain the corresponding 2,3-dicarboxy-5-norbornene-7-acetic acid alkyl ester 2,3-anhydride (III); hydrolizing III to obtain the corresponding 2,3-dicarboxy-5-norbornene-7-acetic acid alkyl ester (IV); treating IV with oxime tetroxide, or with a chlorate salt and a catalytic amount of oxime tetroxide, to obtain the corresponding 2,3-dicarboxy-5,6-dihydroxynorbornene-7-acetic acid alkyl ester (V); treating V with an aldehyde or ketone, preferably acetoacetic acid, to obtain the corresponding 2,3-dicarboxy-5,6-dihydroxynorbornene-7-acetic acid, alkyl ester, acetal or ketal (VI); subjecting VI to electrolysis in a water-pyridine solution containing 1 to 5% of a tertiary amine such as triethylamine to obtain the corresponding 5,6-dihydroxy-2-norbornene-7-acetic acid, alkyl ester acetal or ketal (VII); oxidizing VII with aqueous potassium permanganate and sodium periodate to give the corresponding 2-alkanoyl-3,4-dihydroxy-5-carboxycyclopentanecetic acid, alkyl ester, acetal or ketal (VIII); esterifying (VIII) with an alkanol in the presence of a dehydrating agent such as a carboxylic anhydride or with diazoalkane in the corresponding 2-alkanoyl-3,4-dihydroxy-5-carboxycyclopentanecetic acid, 1,5-dialkyl ester, acetal or ketal (IX) (the two alkyl groups 1 and 5 can be alike or different); reducing IX with an alkali metal borohydride to give the corresponding 2-(1-hydroxyalkyl) - 3,4-dihydroxy-5-carboxycyclopentanecetic acid, 1,5-dialkyl ester, acetal or ketal (X); converting X to a 2-ester, e.g., the methanesulfonate of 2-(1-hydroxyalkyl) - 3,4-dihydroxy-5-carboxycyclopentanecetic acid, 1,5-dialkyl ester, acetal or ketal (XI); treating XI with a dilute aqueous acid to give 2-(1-hydroxyalkyl)-3,4-dihydroxy-5-carboxycyclopentanecetic acid, 1,5-dialkyl ester, 2-ester, e.g., 2-methanesulfonate (XII); oxidizing the glycol XII with aqueous periodate salt to give the corresponding 2-hydroxy-3-(1-hydroxyalkyl) - 5-carboxy - 3,4-dihydro-2H-pyran-4-acetic acid, 4,5-dialkyl ester, 3-ester (XIII); heating compound XIII in a basic medium, pH 7.2 to 9, to give the corresponding compound (XIV), e.g., methyl eledonate when R, R₃ and R₄ are methyl and R₁ is hydrogen. Compound XIV can be selectively hydrolized with dilute mineral acid to an acid of Formula XV. If in Formula XV R₁ and R₂ are methyl and R₃ is hydrogen, the acid is eledonic acid. Alternatively, compound X can be hydrolized with dilute aqueous acid to give compound XII where X₃ is hydroxy.
products were known to be hypertensive and were known to be useful in humans and animals as hypertensive agents (see U.S. Pat. 3,033,877). More recently it was discovered that calcium elonate and other metal elonates and esters of elonlic acid are highly virucidal against Coxsackie A-21 virus, polioviruses 1, 2, and 3, rhinovirus strain 209, parainfluenza-3 virus, herpes viruses, vaccinia virus, adenoviruses 1, 2, 3, and 7, respiratory syncytial virus, Newcastle disease virus and others. Saline solution of 1 mg. per ml. of calcium elonate reduced the viral activity measured by the number of plaques of viruses present in the sample) as follows:

<table>
<thead>
<tr>
<th>Virus</th>
<th>Untreated control</th>
<th>Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newcastle Disease</td>
<td>4.1X10⁶, 2.1X10⁶</td>
<td>1.4X10⁶, 8.5X10⁵</td>
</tr>
<tr>
<td>Polio 1</td>
<td>6.0X10⁵, 2.5X10⁵</td>
<td>6.6X10⁴, 1.2X10⁴</td>
</tr>
<tr>
<td>Polio 2</td>
<td>6.0X10⁵, 2.5X10⁵</td>
<td>2.1X10⁴, 7.6X10³</td>
</tr>
<tr>
<td>Polio 3</td>
<td>6.0X10⁵, 2.5X10⁵</td>
<td>&lt;10⁴, &lt;10³</td>
</tr>
<tr>
<td>Influenza (PR-8)</td>
<td>1.1X10⁶, 6.0X10⁵</td>
<td>&lt;10³, &lt;10³</td>
</tr>
<tr>
<td>Parainfluenza-3</td>
<td>7.5X10⁵</td>
<td>&lt;10³</td>
</tr>
</tbody>
</table>

Likevise, the compounds of Formulas XIII, XIV, and XV and salts thereof are virucidal and are thus useful to clear the equipment or the surgical field of virus contamination used in solutions of 0.1 to 5 parts per 1000 (weight) in the cleaning solution.

In carrying out the process of this invention a cyclo- pentadiene alikali metal salt, e.g., cyclopentadienyl lithium, sodium, or potassium (I) is reacted with a negatively substituted alkyl acetate (A) as defined above, e.g., methyl bromo-, iodo-, or methanesulfonyloxacylate, etyel 2-bromompropionate, and the like. The reaction is preferably carried out by adding to the cyclopentadiene alkali metal salt, in purified tetrahydrofuran, the substituted alkyl acetate, dropwise, in a nitrogen atmosphere, at a temperature of -10 to -30 °C. However, temperatures between 0 °C and -50 °C are operative. Instead of tetrahydrofuran, diethyl, dipropyl, dibutyl ether, or mixed ethers can be used. An average of 70 to 80% yield of 1,3-cyclo-pentadiene-5-acetic acid alkyl ester (II) is obtained, which is used in crude form in the next step.

Compound II in its crude form in tetrahydrofuran or an ether as stated above is reacted with an approximately equimolar amount of alkylmaleic anhydride at a low temperature, between -15 and -50 °C. The reaction period is between 12 hours and 21 days. This process is isolated by conventional procedure, e.g., evaporating the solvent, extraction, crystallization and combinations thereof and is purified by standard methods such as chromatography, recrystallization, and the like to provide the corresponding 2,3-dicarboxy-5-norbornene-7-acetic acid alkyl ester 2,3-anhydride (III).

Compound III is hydrolyzed in conventional manner, such as by heating the compound in aqueous 5% sodium or potassium bicarbonate solution between 10 to 60 minutes on the steam bath, and thereafter acidifying the resulting solution to a pH of 3. The product, a 2,3-dicarboxy-5-norbornene-7-acetic acid alkyl ester (IV) precipitates in the aqueous solution and can be easily collected on a filter. Purification of the product is best achieved by crystallizing the precipitated product.

Compound IV is treated with an alkali metal or alkaline earth carbonate salt, e.g., calcium, or barium chloride) and a catalytic quantity of osmium tetroxide. The reaction can be run in partial suspension through the use of water as reaction medium or in solution through the use of mixed solvents such as water-tert. butyl alcohol or water-tetrahydrofuran, and the like. In the preferred embodiment of this invention compound IV is treated in a water suspension with a 0.1 to 0.5 molar excess of chloride salt and 0.2 to 0.8% by weight of osmium tetroxide. The temperature for the reaction is preferably 40-50 °C, but temperatures between 10 and 75 °C are operative. The reaction time is between 2 and 100 hours and is in general between 5 and 20 hours.

Compound IV can also be oxidized with osmium tetroxide alone, as illustrated in Example 6. The product of the foregoing oxidation, a 2,3-dicarboxy-5,6-dihydroxy-norbornene-7-acetic acid alkyl ester (V) is generally isolated by extraction and the product purified by crystallization.

Compound V is treated with a large excess of an aldehyde or ketone, e.g., acetaldehyde, benzaldehyde, acetone, diethyl ketone, ethyl methyl ketone, dipropyl ketone, acetophenone, or the like in the presence of an anhydrous acid, e.g., hydrogen chloride or hydrogen bromide. In the preferred embodiment of this invention, compound V is treated with a large excess of acetone, which acts as a reagent and slurring agent, in the presence of 5 to 15% of 2,2-dimethoxypropane and 0.1 to 1% of anhydrous hydrogen chloride. The reaction can be carried out at temperatures between 10 to 40 °C during a period of 15 to 120 minutes. The product, a 2,3-dicarboxy-5,6-dihydroxynorbornene-7-acetic acid, alkyl ester (VI) is isolated and purified by conventional procedures, e.g., extraction, crystallization, chromatography and the like.

Compound VII is electrolyzed in a basic medium, e.g., in pyridine-water mixture with 1-5%, triethylamine present, e.g., triethylamine or tributylamine, or heterocyclic tertiary amines such as 1-methylpyridine, 4-methylmorpholine, and 1,4-diaziz(2,2,2) bicyclooctane. The electrodes are preferably platinum and the voltage is held between 50 and 100 volts. The reaction mixture is kept to 20° C. or less during the electrolysis. The electrolysis is advantageously carried out by starting the electrolysis with approximately 20% of the solution to be electrolyzed and then adding the remaining portion slowly so as to maintain the amperage at approximately 4 for a voltage of 80 and a temperature of 20° C. The total reaction time is between 4 to 6 hours. The thus-produced 5,6-dihydroxy-2-norbornene-7-acetic acid, alkyl ester, acetal or ketal (VII) is isolated and purified, preferably by chromatography, recrystallization, extraction, and the like.

Compound VII is oxidized within a pH range 6.0 to 8.5, with an aqueous solution of permanganate and periodate salts, preferably sodium or potassium permanganate and sodium or potassium periodate, with sodium or potassium bicarbonate present. The oxidizing reagents are used in excess of the total osmonos obtained in aqueous concentration of 0.5 to 10% (weight of oxidant to water). The reaction is carried out at temperatures between 10 and 50 °C. during a period of 1 to 8 hours, preferably with stirring. To avoid losses by additional undesired oxidation reactions, the reaction when near completion is terminated by adding sodium sulfite until the permanganate color disappears. The product is preferably isolated by extraction with an organic water-immiscible solvent, e.g., chloroform, methylene chloride, benzene or the like. The thus-obtained 2-alkanoyl-3,4-dihydroxy-5-carboxycyclopentaneacetic acid, alkyl ester, acetal or ketal (VIII) can be purified by crystallization.

The acid compound VIII is esterified by conventional procedures, e.g., with an alkyl and a dehydrating agent such as a carboxilide, e.g., dicyclohexylcarbodiimide, a sulfonl chloride, e.g., p-toluensulfonl chloride, a chloroformate, e.g., isobutyl chloroformate, and the like, or with a diazoalkane in ether to give a dialkyl ester, 2-alanoyl - 3,4 - dihydroxy - 5 - carboxycyclopentaneacetic acid, 1,5-dialkyl ester, acetal or ketal (IX).

Compound IX is then selectively reduced with a metal hydride, preferably a metal borohydride such as lithium, sodium, or potassium borohydride. In the preferred embodiment of this invention the borohydride is used in portions over a short period, 10-30 minutes, to a solution of the diester IX in solution. Methanol, ethanol or ether
are the preferred solvents for compound IX. The thus-obtained compound X, a 2-(1-hydroxyalkyl) -3,4-dihydroxy -5-carboxy-cyclopendane-3,4-acid, 1,5-dialkyl ester, acetal or ketol, is isolated and purified by conventional procedures, e.g., extraction, chromatography, crystallization, and the like.

The hydroxy group of compound X is then esterified, preferably with methanesulfonyl chloride in pyridine solution at a low temperature, for example, between -10 and -15 °C. Other alkane- and alkylbenzene- and benzene-sulfonyl halides can be used, as well as alkyl, benzoyl, and p-toluenyl halides and anhydrides, or brominating and chlorinating agents, e.g., N-bromosuccinimide, N-bromosuccinimide, thionyl chloride and the like. Extraction and recrystallization provide the corresponding 2-(1-hydroxyalkyl)-3,4-dihydroxy-5-carboxy-cyclopendane-3,4-acid, 1,5-dialkyl ester, 2-methanesulfonate, acetal or ketol (XI) or other Formula XI 2-ester.

Compound XI is converted to the corresponding 2-(1-hydroxyalkyl)-3,4-dihydroxy-5-carboxy-cyclopendane-3,4-acid, 1,5-dialkyl ester, 2-ester, e.g., 2-methanesulfonate (XII) by treating it for 1 to 4 hours in aqueous formic acid or in aqueous sulfuric acid, hydrochloric acid or other dilute mineral acids, at a temperature between 10 and 50 °C, preferably at room temperature between 22 and 26 °C. The product XII is recovered by evaporating the reaction mixture, freeze-drying or chromatography.

Compound XII is then treated with excess aqueous alkali metal periodate salt, e.g., sodium or potassium periodate, at a pH between 5 and 7 and at a temperature between 15 and 40 °C. For 1 to 8 hours, usually from 2 to 4 hours at room temperature and the reaction mixture is extracted with a water-immiscible solvent. The extract contains, in solution the corresponding 2-hydroxy-3-(1-hydroxyalkyl) -5-carboxy-3,4-dihydro-2H-pyran-4-acetic acid, 4,5-dialkyl ester, 3-ester, e.g., 3-methanesulfonate (XIII). Compound XIII can be obtained by distillation of the solvent and purified by conventional procedures, e.g., recrystallization, chromatography, and the like.

Heating a mildly basic solution (preferably aqueous pyridine) containing compound XIII at 90-100 °C. For a period of 10 to 300 minutes gives a 3-formyl-5-carboxy-3,4-dihydro-2H-pyran-4-acetic acid, 4,5-dialkyl ester (XIV). In the case that R2, R3, and R4 are methyl and R2 is hydrogen, the product XIV is methyl enolate. Compound XIV is isolated by conventional procedures such as extraction, differential distribution of the product XIV in a solvent system, e.g., Craig extractor or chromatography.

Heating compound XIV with dilute mineral acid, e.g., 0.1 M sulfuric acid gives 3-formyl-5-carbalkoxy-3,4-dihydro-2H-pyran-4-acetic acid (XV), which in case R2 and R3 are methyl and R4 is hydrogen is free enolic acid.

The following Preparation and Examples illustrate this invention.

**PREPARATION 1**

**Cyclopentadienyl sodium**

Metallic sodium (23 g; 1 mole) was pressed into a fine ribbon and suspended in freshly purified tetrahydrofuran. A 100 ml quantity of cyclopenta-1,2,3-triene was added in one portion and the mixture was stirred under nitrogen for 45 minutes. During that period a vigorous reaction occurred, warming the mixture to reflux. After this time an outside heat source was applied and the reaction mixture was heated under reflux an additional 2 hours. By this time all of the sodium had reacted. The cyclopentadienyl sodium is extremely sensitive to air and depending on the care with which the reaction was run, at this point it showed variation from near colorless through pink to deep purple. The color did not seem to appreciably affect the yields.

In the same manner given above cyclopentadienyl lithium or potassium can be made.

**EXAMPLE 1**

**Methyl 1,3-cyclopenta-1,2-diene-5-acetate**

One mole of cyclopentadienyl sodium, made up with tetrahydrofuran to 1 liter was cautiously transferred, under a nitrogen atmosphere, to a dropping funnel and was then added dropwise over 1.5 hours to 304 g. (2.0 moles) of methyl bromoacetate cooled to -20 °C. During the addition, the reaction mixture was maintained between -20 and -15 °C. The crude reaction mixture was used as such for the subsequent step. The product was analyzed by withdrawing an aliquot, filtering and distilling the tetrahydrofuran from the aliquot filtrate at >-10 °C under high vacuum. The residue was quickly dissolved in deuterochloroform and an NMR taken. Analyses of various runs of the reaction have indicated 70-80% of the desired isomer (methyl 1,3-cyclopenta-1,2-diene-5-acetate) and 30-20% of the 1-isomer (methyl 1,3-cyclopenta-1,2-diene-1-acetate).

NMR spectrum (CDCl3): (a) 5-isomer = 2.38 (2H, d, J = 8.5 cpm), 3.67 (3H, s), 6.42 (4H, s).

(b) 1-isomer = 3.00 (2H, m), 3.44 (2H, m), 3.65 (3H, s), 6.38 (3H, m).

The same product is obtained by replacing the cyclopentadienyl sodium with cyclopentadienyl lithium or potassium.

**EXAMPLE 2**

**Ethyl a-methyl-1,3-cyclopenta-1,2-diene-5-acetate**

In the manner given in Example 1, cyclopentadienyl sodium was added to ethyl a-bromopropionate to give ethyl a-methyl-1,3-cyclopenta-1,2-diene-5-acetate.

In the same manner given in Example 1, other alkyl 1,3-cyclopenta-1,2-diene-5-acetates and alkyl a-alkyl-1,3-cyclopenta-1,2-diene-5-acetates (II) can be made by reacting an alkyl a-bromotetrafluoro-alkane (A) with cyclopentadienyl anions.

Representative compounds, thus obtained, include: propyl a-ethyl-1,3-cyclopenta-1,2-diene-5-acetate, butyl a-propyl-1,3-cyclopenta-1,2-diene-5-acetate, pentyl a-buty1-1,3-cyclopenta-1,2-diene-5-acetate, hexyl a-methyl-1,3-cyclopenta-1,2-diene-5-acetate, heptyl 1,3-cyclopenta-1,2-diene-5-acetate, octyl 1,3-cyclopenta-1,2-diene-5-acetate, isopropyl a-methyl-1,3-cyclopenta-1,2-diene-5-acetate, isobutyl a-propyl-1,3-cyclopenta-1,2-diene-5-acetate, and the like.

**EXAMPLE 3**

**Methyl 2,3-dicarboxy-2-methyl-5-norborne-7-acetate, 2,3-anhydride**

The total crude reaction mixture containing methyl 1,3-cyclopentadiene-5-acetate (Example 1) from a 1.5-mole run was treated with 500 g. (4.4 moles) of citric anhydride. After distillation of excess solvent at less than -10 °C and less than 1 mm, the reaction mixture was allowed to stand 14 days at -13 °C. The reaction mixture was then partitioned between methylene chloride and water. The methylene chloride solution was thoroughly washed successively with 5% aqueous sodium bicarbonate solution, water, and saturated brine. The methylene chloride solution was then dried over anhydrous sodium sulfate and distilled in vacuo, leaving a viscous brown residue. Crystallization of the residue from ether gave 147.5 g. of methyl 2,3-dicarboxy-2-methyl-5-norborne-7-acetate, 2,3-anhydride of melting point 100-103 °C. There was obtained from the mother liquor a second crop amounting to 24.3 g; melting point 90-105 °C.
A sample was prepared for analysis by one more crystallization from methylene chloride-ether; melting point 105-108° C.

**Analysis.**—Calcd. for C_{9}H_{8}O_{6} (percent): C, 62.39; H, 5.64. Found (percent): C, 62.28; H, 5.97.

NMR spectrum (CDCl_{3}, δ): 1.66 (3H, s), 2.41 (2H, A_{3}B), 2.61 (1H, A), 3.01 (1H, m.), 3.22 (1H, d, J = 4 cps.), 3.65 (3H, s), 6.30 (2H, AA'XX').

**Example 4**

**Ethyl 2,3-dicarboxy-2-methyl-5-norbornene-7-acetate 2,3-anhydride**

In the manner given in Example 3, ethyl 1,3-cyclopentadiene-5-acetate was reacted with citraconic anhydride to give ethyl 2,3-dicarboxy-2-methyl-5-norbornene-7-acetate 2,3-anhydride.

In the manner given in Examples 3 and 4, other alkyl 2,3-dicarboxy-2-alkyl and alkyl α-alkyl-2,3-dicarboxy-2-alkyl-5-norbornene-7-acetate 2,3-anhydrides can be produced by reacting a selected alkyl 1,3-cyclopentadiene-5-acetate or alkyl α-alkyl-1,3-cyclopentadiene-5-acetate with an alkylmaleic anhydride. Representative compounds, thus produced, include:

- ethyl α-methyl-2,3-dicarboxy-2-methyl-5-norbornene-7-acetate 2,3-anhydride,
- propyl α-ethyl-2,3-dicarboxy-2-propyl-5-norbornene-7-acetate 2,3-anhydride,
- butyl α-propyl-2,3-dicarboxy-2-butyl-5-norbornene-7-acetate 2,3-anhydride,
- isopropyl α-butyl-2,3-dicarboxy-2-isopropyl-5-norbornene-7-acetate 2,3-anhydride,
- isobutyl α-isobutyl-2,3-dicarboxy-2-isobutyl-5-norbornene-7-acetate 2,3-anhydride,
- hexyl α-propyl-2,3-dicarboxy-2-methyl-5-norbornene-7-acetate 2,3-anhydride,
- heptyl α-isopropyl-2,3-dicarboxy-2-methyl-5-norbornene-7-acetate 2,3-anhydride,
- octyl α-methyl-2,3-dicarboxy-2-methyl-5-norbornene-7-acetate 2,3-anhydride,
- pentyl 2,3-dicarboxy-2-ethyl-5-norbornene-7-acetate 2,3-anhydride,
- isopentyl 2,3-dicarboxy-2-methyl-5-norbornene-7-acetate 2,3-anhydride,
- methyl α-ethyl-2,3-dicarboxy-2-methyl-5-norbornene-7-acetate 2,3-anhydride,
- ethyl α-ethyl-2,3-dicarboxy-2-butyl-5-norbornene-7-acetate 2,3-anhydride,

and the like.

**Example 7**

**Methyl 2,3-dicarboxy-2-methyl-5-norbornene-7-acetate**

In the manner given in Example 4, 1 mole of methyl 1,3-cyclopentadiene-5-acetate was reacted with 340 g. of citraconic anhydride in tetrahydrofuran.

The tetrahydrofuran was removed by distillation in vacuo at >10° C. The reaction mixture was allowed to stand for 3 days at −13° C. and 2 days at −2° C. The mixture was then poured into 1 liter of water containing 320 g. of sodium carbonate. The resultant mixture was cautiously heated on a steam bath for 1 hour. It was then cooled, extracted with methylene chloride, and then acidified with concentrated hydrochloric acid. The precipitated product was collected by filtration and washed with water. Crystallization of the product from water gave 38.0 g. of methyl 2,3-dicarboxy-2-methyl-5-norbornene-7-acetate of melting point 150-151° C. Second and third crops totaling 16.1 g. were obtained; melting point 139-143° C.

**Example 8**

**Methyl 2,3-dicarboxy-5,6-dihydroxy-2-methylnorbornene-7-acetate**

A 106 g. (0.396 mole) quantity of methyl 2,3-dicarboxy-2-methyl-5-norbornene-7-acetate was dissolved in 750 ml. of tetrahydrofuran and the resultant solution was treated with 100 g. (0.394 mole) of osmium tetroxide in 750 ml. of tetrahydrofuran. The mixture was allowed to stand for three days at 25° C. The resultant black mixture was cooled in an ice bath, stirred and treated with excess hydrogen sulfide gas. The mixture was filtered free of solids. The filter cake was washed thoroughly with tetrahydrofuran. The filtrate and the washes were combined and evaporated to dryness. Crystallization of the residue from ethyl acetate gave 63.8 g. of methyl 2,3-dicarboxy-5,6-dihydroxy-2-methylnorbornene-7-acetate as off-white crystals of melting point 121-127° C. There was obtained from the mother liquors a second crop amounting to 7.0 g. of product. Total yield 59%. A sample was prepared for analysis by recrystallization from water; melting point 122-126° C.

**Analysis.**—Calcd. for C_{9}H_{8}O_{6} (percent): C, 58.20; H, 6.01. Found (percent): C, 58.16; H, 6.10.

**Example 6**

**Ethyl 2,3-dicarboxy-2-methyl-5-norbornene-7-acetate**

In the manner given in Example 5, ethyl 2,3-dicarboxy-2-methyl-5-norbornene-7-acetate 2,3-anhydride was hydrolyzed in water to give ethyl 2,3-dicarboxy-2-methyl-5-norbornene-7-acetate.

In the manner given in Example 5, other alkyl 2,3-dicarboxy-5-norbornene-7-acetate 2,3-anhydrides of For...
Methyl 2,3-dicarboxy-5,6-dihydroxy-2-methylnorbornane-7-acetate

A 5.0 g. (19 millimoles) quantity of methyl 2,3-dicarboxy-2-methyl-5-norbornene-7-acetate was added to a solution of 3.0 g. (24.5 millimoles) of potassium chloride and 50 mg. of osmium tetroxide in 125 ml. of water. The mixture was warmed to 50°C and stirred for 5 hours. The reaction mixture was then cooled and extracted with benzene. The aqueous layer was saturated with sodium chloride and extracted 3 times with tetrahydrofuran. The tetrahydrofuran solution was dried over anhydrous magnesium sulfate and distilled in vacuo, leaving an oil. Crystallization of the oil from ethyl acetate gave 1.95 g. of methyl 2,3-dicarboxy-5,6-dihydroxy-2-methylnorbornane-7-acetate; melting point 129-130°C.

Example 10

Ethyl 2,3-dicarboxy-5,6-dihydroxy-2-ethylnorbornane-7-acetate

In the manner given in Example 9, ethyl 2,3-dicarboxy-2-ethyl-5-norbornene-7-acetate was treated with osmium tetroxide in tetrahydrofuran to give ethyl 2,3-dicarboxy-5,6-dihydroxy-2-ethylnorbornane-7-acetate.

In the manner given in Example 9, other alkyl 2,3-dicarboxy-5,6-dihydroxy-2-norbornane-7-acetates are produced by treating the corresponding alkyl 2,3-dicarboxy-2-alkyl-5-norbornene-7-acetates with osmium tetroxide. Representative compounds, thus prepared, include:

ethyl 2,3-dicarboxy-5,6-dihydroxy-2-methylnorbornane-7-acetate,
propyl 2,3-dicarboxy-5,6-dihydroxy-2-propynorbornane-7-acetate,
butyl 2,3-dicarboxy-5,6-dihydroxy-2-butynorbornane-7-acetate,
isopropyl 2,3-dicarboxy-5,6-dihydroxy-2-isobutylnorbornane-7-acetate,
isobutyl 2,3-dicarboxy-5,6-dihydroxy-2-isopropynorbornane-7-acetate,
hexyl α-propyl-2,3-dicarboxy-5,6-dihydroxy-2-methylnorbornane-7-acetate,
heptyl 2,3-dicarboxy-5,6-dihydroxy-2-ethylnorbornane-7-acetate,
octyl α-propyl-2,3-dicarboxy-5,6-dihydroxy-2-propynorbornane-7-acetate,
pentyl 2,3-dicarboxy-5,6-dihydroxy-2-ethylnorbornane-7-acetate,
isopentyl 2,3-dicarboxy-5,6-dihydroxy-2-methylnorbornane-7-acetate,
methyl α-propyl-2,3-dicarboxy-5,6-dihydroxy-2-methylnorbornane-7-acetate,
ehtyl α-ethyl-2,3-dicarboxy-5,6-dihydroxy-2-butynorbornane-7-acetate,
and the like.

Example 11

Methyl 2,3-dicarboxy-5,6-dihydroxy-2-methylnorbornane-7-acetate acetone

A 128 g. (0.424 mole) quantity of methyl 2,3-dicarboxy-5,6-dihydroxy-2-methylnorbornane - 7 - acetate was slurried in 2 l. of acetone and 160 ml. of 2.2-dimethoxypropane. The slurry was treated with 4 ml. of 2.4 M hydrogen chloride in anhydrous dioxane, causing the suspended solid to dissolve immediately. After 1/2 hour, the solution was evaporated to dryness in vacuo leaving, when completely dry, 140 g. of crystals of methyl 2,3-dicarboxy-5,6-dihydroxy-2-methylnorbornane-7-acetate, acetone suitable for further use. A sample was prepared for analysis by one recrystallization from benzene-acetone; melting point 154-155°C.

Analysis.—Calcd. for C_{16}H_{22}O_5 (percent): C, 56.15; H, 6.48. Found (percent): C, 56.25; H, 6.57.

Example 12

Methyl α-methyl-2,3-dicarboxy-5,6-dihydroxy-2-methylnorbornane-7-acetate acetone

In the manner given in Example 11, methyl α-methyl-2,3-dicarboxy-5,6-dihydroxy-2-methylnorbornane-7-acetate was treated with 2,2-dimethoxypropane in acetone to give methyl α-methyl-2,3-dicarboxy-5,6-dihydroxy-2-methylnorbornane-7-acetate acetone.

In the manner given in Example 11, other alkyl 2,3-dicarboxy-5,6-dihydroxy-2-alkylnorbornane-7-acetate acid ketals or acetals can be prepared by reacting an alkyl 2,3-dicarboxy-5,6-dihydroxy-2-alkynorbornane-7-acetate with a ketone or aldehyde. Representative compounds, thus obtained, include:

the acetonide, methyl ethyl ketal, diethyl ketal, propyl ethyl ketal, formaldehyde acetal, acetaldehyde acetal, and propionaldehyde acetal and the like of
ethyl 2,3-dicarboxy-5,6-dihydroxy-2-methylnorbornane-7-acetate,
propyl 2,3-dicarboxy-5,6-dihydroxy-2-propynorbornane-7-acetate,
butyl α-propyl-2,3-dicarboxy-5,6-dihydroxy-2-butynorbornane-7-acetate,
isopropyl α-butyl-2,3-dicarboxy-5,6-dihydroxy-2-isobutylnorbornane-7-acetate,
isobutyl 2,3-dicarboxy-5,6-dihydroxy-2-isopropynorbornane-7-acetate,
hexyl α-propyl-2,3-dicarboxy-5,6-dihydroxy-2-methylnorbornane-7-acetate,
heptyl 2,3-dicarboxy-5,6-dihydroxy-2-ethylnorbornane-7-acetate,
ocyl α-propyl-2,3-dicarboxy-5,6-dihydroxy-2-propynorbornane-7-acetate,
pentyl 2,3-dicarboxy-5,6-dihydroxy-2-ethylnorbornane-7-acetate,
isopentyl 2,3-dicarboxy-5,6-dihydroxy-2-methylnorbornane-7-acetate,
methyl α-propyl-2,3-dicarboxy-5,6-dihydroxy-2-methylnorbornane-7-acetate,
ehtyl α-ethyl-2,3-dicarboxy-5,6-dihydroxy-2-butynorbornane-7-acetate,
and the like.

Example 13

Methyl 2-methyl-5,6-dihydroxy-2-norbornene - 7 - acetate acetone (VII when R_1, R_2, R_3 and R_4 are methyl; R_5 is hydrogen)

A 5.1 g. (15 millimoles) quantity of methyl 2,3-dicarboxy-5,6-dihydroxy-2-methylnorbornane-7-acetate acetone was dissolved in 200 ml. of pyridine: water (90:10 by volume) and 3.75 ml. of triethylamine. The resultant solution was electrolyzed using platinum wire mesh electrodes held between 60 and 90 volts. The reaction temperature was maintained throughout at 15-20°C. Using a solid carbon dioxide-acetone bath. The initial value for the amperage under these conditions was 4. The amperage was maintained at this value by the gradual addition of a solution of 20.5 g. of methyl 2,3-dicarboxy-5,6-dihydroxy-2-methylnorbornane-7-acetate acetone in 100 ml. of pyridine:water (90:10 by volume) and 3.75 ml. of triethylamine. The addition was completed in about 1.5 hours, after which the reaction was allowed to proceed till the amperage fell below a value of one (about 5 hours total reaction time). The mixture was evaporated to dryness in vacuo and the residue was partitioned between 1 N hydrochloric acid and methylene chloride. The methylene
chloride layer was washed successively with 1 N hydrochloric acid, 5% aqueous sodium bicarbonate and saturated brine, and dried over anhydrous sodium sulfate. Distillation of the methylene chloride left a dark brown residue which was combined with the crude residues from two similar runs. Chromatography on 2 kg. of silica gel, eluting with methanol:methylene chloride (3:97 by volume) gave two compounds. The faster moving was easily detectable on thin layer chromatography with KMnO₄-NaOH reagent and was found by NMR to be the desired methyl 2-methyl-5,6-dihydroxy-2-norborenone-7-acetate acetonide.

The yields of this compound varied from 25% on the scale described above to greater than 50% on gram runs.

IR spectrum (mineral oil mull): 1735, 1625, 1265, 1200, 1180, 1030, 1030, 855.

**Example 14**

**Methyl 2,2-dimethyl-5,6-dihydroxy-2-norborenone-7-acetate acetonide**

In the manner given in Example 13, methyl 2,2-dimethyl-2,3-dicarboxy-5,6-dihydroxynorbornene-7-acetate acetonide was decarboxylated in pyridine-water in the presence of triethylamine, with an electric current, to give methyl 2,2-dimethyl-5,6-dihydroxy-2-norborenone-7-acetate acetonide.

In the manner given in Example 13, other alkyl 2,3-dicarboxy-5,6-dihydroxynorbornene-7-acetate ketals or acetals can be converted to the corresponding alkyl 2,3-dicarboxy-5,6-dihydroxy-2-norborenone-7-acetate ketals or acetals by means of electric current.

Representative compounds, thus obtained, include:

- ethyl 2,2-diethyl-5,6-dihydroxy-2-norborenone-7-acetate acetonide,
- propyl 2,2-dipropyl-5,6-dihydroxy-2-norborenone-7-acetate acetonide,
- butyl 2,2-dibutyl-5,6-dihydroxy-2-norborenone-7-acetate acetonide,
- isopropyl 2,2-dimethyl-5,6-dihydroxy-2-norborenone-7-acetate benzaldehyde acetal,
- isobutyl 2-methyl-2-ethyl-5,6-dihydroxy-2-norborenone-7-acetate diethyl ketone ketal,
- pentyl 2-ethyl-2-propyl-5,6-dihydroxy-2-norborenone-7-acetate methyl ethyl ketone ketal,
- hexyl 2-propyl-2-butyl-5,6-dihydroxy-2-norborenone-7-acetate formaldehyde acetate,
- heptyl 2-isopropyl-2-isobutyl-5,6-dihydroxy-2-norborenone-7-acetate formaldehyde acetate,
- octyl 2-butyl-2-propyl-5,6-dihydroxy-2-norborenone-7-acetate methyl butyl ketone ketal,
- isopentyl 2-butyl-2-methyl-5,6-dihydroxy-2-norborenone-7-acetate propionlaldehyde acetate,
- methyl 2-ethyl-2-methyl-5,6-dihydroxy-2-norborenone-7-acetate acetonide,
- ethyl 2-propyl-2-methyl-5,6-dihydroxy-2-norborenone-7-acetate acetonide,
- propyl 2-isopropyl-2-ethyl-5,6-dihydroxy-2-norborenone-7-acetate acetonide,
- ethyl 2,2-dibutyl-5,6-dihydroxy-2-norborenone-7-acetate acetonide,
- and the like.

**Example 15**

**Methyl 2-acetyl-3,4-dihydroxy-5-carboxycyclopenteneacetate acetate acetonide**

A quantity of 9.6 g. (38 millimoles) of methyl 2-acetyl-5,6-dihydroxy-2-norborenone-7-acetate acetonide was treated with 9.6 g. of solid sodium bicarbonate followed by 960 ml. of an aqueous solution containing 46.4 g. (218 millimoles) of sodium peridate and 0.9 g. (5.7 millimoles) of potassium permanagante. The reaction mixture was stirred vigorously for 4½ hours. The mixture was then cooled in an ice-bath and solid sodium sulfite slowly added until the potassium permanagante color disappeared. This solution was then extracted with methylene chloride. The aqueous layer was acidified to pH 2 and extracted 3 times with methylene chloride. The combined methylene chloride solutions were washed with saturated brine and dried over anhydrous sodium sulfate. Distillation of the methylene chloride in vacuo left 6.9 g. of oil which solidified on standing. Crystallization of this material from benzene-Skellysolve B hexanes gave 4.1 g. of crystalline methyl 2-acetyl-3,4-dihydroxy-5-carboxycyclopenteneacetate acetonide; melting point 87-89° C. A second and third crop were obtained and combined, giving another 1.0 g.; melting point 87-93° C. A sample was prepared for analysis by one further crystallization from benzene-Skellysolve B hexanes; melting point 91-93° C. Analysis — Calcd. for C₁₆H₂₄O₇ (percent): C, 55.99; H, 6.71. Found (percent): C, 55.71; H, 7.00.

**Example 16**

**Methyl 2-acetyl-3,4-dihydroxy-5-carboxycyclopenteneacetate acetonide**

In the manner given in Example 15, methyl 2-acetyl-5,6-dihydroxy-2-norborenone-7-acetate acetonide was converted with sodium bicarbonate, sodium peridate and potassium permanganate to methyl 2-acetyl-3,4-dihydroxy-5-carboxycyclopenteneacetate acetonide.

In the same manner given in Example 15, other alkyl 2-alkyl-5,6-dihydroxy-2-norborenone-7-acetate acetals and ketals are converted to the corresponding alkyl 2-alkanoyl-3,4-dihydroxy-5-carboxycyclopenteneacetate acetalts and ketals.

Representative compounds, thus produced, include:

- ethyl 2-ethyl-2-propionyl-3,4-dihydroxy-5-carboxycyclopenteneacetate acetonide,
- propyl 2-propyl-2-butyl-3,4-dihydroxy-5-carboxycyclopenteneacetate acetonide,
- butyl 2-butyl-2-valeryl-3,4-dihydroxy-5-carboxycyclopenteneacetate acetonide,
- isopropyl 2-acetyl-2-ethyl-3,4-dihydroxy-5-carboxycyclopenteneacetate benzaldehyde acetal,
- isobutyl 2-ethyl-2-butyl-3,4-dihydroxy-5-carboxycyclopenteneacetate diethyl ketone ketal,
- pentyl 2-propyl-2-valeryl-3,4-dihydroxy-5-carboxycyclopenteneacetate methyl ethyl ketone ketal,
- hexyl 2-isopropyl-2-isobutyl-3,4-dihydroxy-5-carboxycyclopenteneacetate formaldehyde acetate,
- heptyl 2-isopropyl-2-isobutyl-3,4-dihydroxy-5-carboxycyclopenteneacetate formaldehyde acetate,
- octyl 2-butyl-2-propyl-3,4-dihydroxy-5-carboxycyclopenteneacetate acetonide,
- isopentyl 2-butyl-2-methyl-3,4-dihydroxy-5-carboxycyclopenteneacetate methyl butyl ketone ketal,
- isopentyl 2-butyl-2-methyl-3,4-dihydroxy-5-carboxycyclopenteneacetate methyl butyl ketone ketal,
- ethyl 2-propyl-2-methyl-3,4-dihydroxy-5-carboxycyclopenteneacetate methyl butyl ketone ketal,
- propyl 2-isopropyl-2-ethyl-3,4-dihydroxy-5-carboxycyclopenteneacetate methyl butyl ketone ketal,
- ethyl 2-propionyl-2-propionyl-3,4-dihydroxy-5-carboxycyclopenteneacetate acetonide,
- propyl 2-propionyl-3,4-dihydroxy-5-carboxycyclopenteneacetate acetonide,
- ethyl 2-butyl-2-valeryl-3,4-dihydroxy-5-carboxycyclopenteneacetate acetonide,
- and the like.

**Example 17**

2-acetyl-3,4-dihydroxy-5-carboxycyclopentaneacetic acid 1,3-dimethyl ester, acetonide

A 4.1 g. sample of methyl 2-acetyl-3,4-dihydroxy-5-carboxycyclopentancetate acetate in ethanol and treated with excess ethereal diazomethane. The solution was then evaporated to dryness, leaving 4.3 g. of colorless oil, suitable for the next reaction. A small sample was chromatographed on silica gel. The desired material was eluted with methanol: methylene chloride (2.5:97.5 by volume). Distillation of the solvent from
the center fractions containing the product as indicated by thin layer chromatography left an oil, 2-acytethyl-3,4-dihydroxy-5-carboxycyclopentanecetic acid 1,5-dimethyl ester, acetoniode.

**Example 18**

a-Methyl-2-acytethyl-3,4-dihydroxy-5-carboxycyclopentanecetic acid 1,5-dimethyl ester, acetoniode

In the manner given in Example 17, methyl a-methyl-2-acytethyl-3,4-dihydroxy - 5 - carboxycyclopentanecetate acetoniode was treated with excess diazomethane in diethyl ether to give a methyl-2-acytethyl-3,4-dihydroxy-5-carboxycyclopentanecetic acid 1,5-dimethyl ester, acetoniode.

In the manner given in Example 17, other 2-alkanoyl-3,4-dihydroxy-5-carboxycyclopentanecetic acid 1,5-dialkyl ester acetals or ketals can be produced by reacting a selected alkyl 2-alkanoyl-3,4-dihydroxy - 5 - carboxycyclopentanecetate acetal or ketal with a diazoalkane. Representative compounds, thus obtained, include:

- ethyl-2-propionyl-3,4-dihydroxy-5-carboxycyclopentanecetic acid 1,5-dimethyl ester, acetoniode
- propyl-2-butyryl-3,4-dihydroxy-5-carboxycyclopentanecetic acid 1-ethyl-5-propyl ester, acetoniode
- butyl-2-valeryl-3,4-dihydroxy-5-carboxycyclopentanecetic acid 1-methyl-5-ethyl ester, acetoniode
- methyl-2-acytethyl-3,4-dihydroxy-5-carboxycyclopentanecetic acid 1-butyl-5-methyl ester, benzaldehyde acetal
- 2-acytethyl-3,4-dihydroxy-5-carboxycyclopentanecetic acid 1-propyl-5-ethyl ester, diethyl ketone ketal
- methyl-2-valeryl-3,4-dihydroxy-5-carboxycyclopentanecetic acid 1-heptyl-5-propyl ester, methyl ethyl ketone ketal
- ethyl-2-acytethyl-3,4-dihydroxy-5-carboxycyclopentanecetic acid 1-octyl-5-butyl ester, formaldehyde acetal
- propyl-2-valeral-3,4-dihydroxy-5-carboxycyclopentanecetic acid 1-isobutyl-5-methyl ester, acetoniode
- isopropyl-2-isobutyryl-3,4-dihydroxy-5-carboxycyclopentanecetic acid 1-isobutyl-5-ethyl ester, butyl ketone ketal
- butyl-2-butyryl-3,4-dihydroxy-5-carboxycyclopentanecetic acid 1-pentyl-5-butyl ester, propionaldehyde acetal
- butyl-2-valeryl-3,4-dihydroxy-5-carboxycyclopentanecetic acid 1-heptyl-5-propyl ester, acetoniode
- propyl-2-acytethyl-3,4-dihydroxy-5-carboxycyclopentanecetic acid 1-octyl-5-propyl ester, acetoniode
- isopropyl-2-isobutyryl-3,4-dihydroxy-5-carboxycyclopentanecetic acid 1-isobutyl-5-ethyl ester, acetoniode
- butyl-2-acytethyl-3,4-dihydroxy-5-carboxycyclopentanecetic acid 1-butyl-5-propyl ester, acetoniode
- and the like.

**Example 19**

2-(1-hydroxyethyl)-3,4-dihydroxy-5-carboxycyclopentanecetic acid 1,5-dimethyl ester, acetoniode

3.7 g. (11.8 millimoles) quantity of 2-acytethyl-3,4-dihydroxy - 5 - carboxycyclopentanecetic acid 1,5-dimethyl ester, acetoniode, was dissolved in 20 ml. of methanol and the solution was cooled to 0° C. in an ice-salt bath. Over a period of 15 minutes, 334 mg. of sodium borohydrate was added. After a total of 60 minutes, 0.53 ml. of acetic acid was added and the solution was evaporated to dryness. The residue was partitioned between methylene chloride and water. The methylene chloride layer was separated and combined with a methylene chloride wash of the water layer. The methylene chloride solution was washed with saturated brine and dried over anhydrous sodium sulfate. Distillation of the methylene chloride in vacuo left an essentially quantitative yield of oily residue, which was shown by NMR spectroscopy not to contain any detectable starting material but rather showed the product to consist of a nearly equal mixture of the diastereomeric alcohols, 2-(1-hydroxyethyl)-3,4-dihydroxy-5-carboxycyclopentanecetic acid 1,5-dimethyl ester, acetoniode.

**Example 20**

α-Methyl-2-(1-hydroxyethyl)-3,4-dihydroxy - 5 - carboxycyclopentanecetic acid 1,5-dimethyl ester, acetoniode

In the manner given in Example 19, α-methyl-2-acytethyl-3,4-dihydroxy-5-carboxycyclopentanecetic acid 1,5-dimethyl ester, acetoniode was reduced with sodium borohydrate to give a mixture of the two diastereomeric alcohols, α-methyl-2-(1-hydroxyethyl)-3,4-dihydroxy-5-carboxycyclopentanecetic acid 1,5-dimethyl ester, acetoniode.

In the same manner given in Example 19, other 2-(1-hydroxyalkyl)-3,4-dihydroxy-1,5-dialkyl ester, acetals or ketals can be prepared by reducing the corresponding 2-alkanoyl-3,4-dihydroxy-5-carboxycyclopentanecetic acid 1,5-dialkyl ester, acetals or ketals with an alkali metal borohydride. Representative compounds, thus prepared include:

- ethyl-2-(hydroxypropyl)-3,4-dihydroxy-5-carboxycyclopentanecetic acid 1,5-diethyl ester, acetoniode
- propyl-2-(1-hydroxybutyl)-3,4-dihydroxy-5-carboxycyclopentanecetic acid 1,5-diethyl ester, acetoniode
- butyl-2-(1-hydroxypentyl)-3,4-dihydroxy-5-carboxycyclopentanecetic acid 1-ethyl-5-propyl ester, acetoniode
- methyl-2-(1-hydroxyethyl)-3,4-dihydroxy-5-carboxycyclopentanecetic acid 1-methyl-5-ethyl ester, benzaldehyde acetal
- 2-(1-hydroxyethyl)-3,4-dihydroxy-5-carboxycyclopentanecetic acid 1-butyl-5-methyl ester, diethyl ketone ketal
- methyl-2-(1-hydroxypentyl)-3,4-dihydroxy-5-carboxycyclopentanecetic acid 1-propyl-5-ethyl ester, methyl ethyl ketone ketal
- ethyl-2-(1-hydroxypentyl)-3,4-dihydroxy-5-carboxycyclopentanecetic acid 1-heptyl-5-propyl ester, formaldehyde acetal
- propyl-2-(1-hydroxypentyl)-3,4-dihydroxy-5-carboxycyclopentanecetic acid 1-octyl-5-butyl ester, acetoniode
- isopropyl-2-(1-hydroxy-2-methylpropyl)-3,4-dihydroxy-5-carboxycyclopentanecetic acid 1-isopropyl-5-methyl ester, methyl butyl ketone ketal
- butyl-2-(1-hydroxybutyl)-3,4-dihydroxy-5-carboxycyclopentanecetic acid 1-isobutyl-5-ethyl ester, propionaldehyde acetal
- ethyl-2-(1-hydroxypentyl)-3,4-dihydroxy-5-carboxycyclopentanecetic acid 1-pentyl-5-butyl ester, acetoniode
- propyl-2-(1-hydroxyethyl)-3,4-dihydroxy-5-carboxycyclopentanecetic acid 1-heptyl-5-propyl ester, acetoniode
- isopropyl-2-(1-hydroxy-2-methylpropyl)-3,4-dihydroxy-5-carboxycyclopentanecetic acid 1-octyl-5-propyl ester, acetoniode
- butyl-2-(1-hydroxyethyl)-3,4-dihydroxy-5-carboxycyclopentanecetic acid 1-pentyl-5-methyl ester, acetoniode
- and the like.

**Example 21**

2-(1-hydroxyethyl)-3,4-dihydroxy-5-carboxycyclopentanecetic acid 1,5-dimethyl ester, acetoniode; and 2-(1-hydroxyethyl)-3,4-dihydroxy-5-carboxycyclopentanecetic acid 1,5-dimethyl ester, 2-acetate, acetoniode

A 0.70 g. (2.2 millimoles) quantity of 2-(1-hydroxyethyl)-3,4-dihydroxy-5-carboxycyclopentanecetic acid 1,5-dimethyl ester, acetoniode was dissolved in 10 ml. of pyridine and the solution was cooled to about 0° C. This solution was treated with 1.14 g. (10 millimoles) of methanesulfonyl chloride. After standing 18 hours at -2° C., the reaction mixture was treated with about
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1 ml of water and the mixture was allowed to stand for 10 minutes. The mixture was poured into methylene chloride and extracted with 1 N hydrochloric acid, 5% aqueous sodium bicarbonate, and saturated brine. The methylene chloride solution was dried over anhydrous sodium sulfate and distilled in vacuo, leaving 0.865 g. of oil. NMR showed this material to be a nearly equal mixture of the mesylates of the diastereomeric alcohols. On standing, the above oil crystallized. Recrystallization of the material from benzene-Skellysolve B hexanes gave 160 mg. of needles of melting point 99–103° C. A second crop was obtained from ether, amounting to 138 mg. of melting point 97–102° C. Recrystallization of combined crops 1 and 2 from benzene-Skellysolve B hexanes gave 180 mg. of needles of 2-(1-hydroxyethyl)-3,4-dihydroxy-5-carboxycyclopentanecarboxylic acid 1,5-dimethyl ester, 2-methanesulfonate, acetoinide of melting point 102–103° C. Analyzed.—Calcd. for C_{16}H_{24}O_{8} (percent): C, 48.72; H, 6.65; S, 8.13. Found (percent): C, 48.82; H, 6.28; S, 7.94.

IR spectrum (mineral oil mull): 1735, 1695 w, 1385, 1350, 1355, 1285, 1270, 1230, 1200, 1180, 1150, 1090, 1060, 985, 970, 900, 800, 810.

In a similar manner, but using acetic anhydride instead of methanesulfonyl chloride, there was prepared 2-(1-hydroxyethyl)-3,4-dihydroxy-5-carboxycyclopentanecarboxylic acid 1,5-dimethyl ester, 2-acetate, acetoinide; melting point, 85–86.5° C.

Analyzed.—Calcd. for C_{16}H_{24}O_{8} (percent): C, 56.97; H, 7.51. Found (percent): C, 57.22; H, 7.45.

EXAMPLE 22

α-Methyl-2-(1-hydroxyethyl)-3,4-dihydroxy-5-carboxycyclopentanecarboxylic acid 1,5-dimethyl ester, 2-methanesulfonate, acetoinide

In the manner given in Example 21, α-methyl-2-(1-hydroxyethyl)-3,4-dihydroxy-5-carboxycyclopentanecarboxylic acid 1,5-dimethyl ester, acetoinide was treated with methanesulfonyl chloride in pyridine to give α-methyl-2-(1-hydroxyethyl)-3,4-dihydroxy-5-carboxycyclopentanecarboxylic acid 1,5-dimethyl ester, 2-methanesulfonate, acetoinide.

In the manner given in Example 21, other 2-(1-hydroxyalkyl)-3,4-dihydroxy-5-carboxycyclopentanecarboxylic acid 1,5-dialkyl ester, 2-methanesulfonate, acetals or ketals can be prepared by treating the corresponding 2-(1-hydroxyalkyl)-3,4-dihydroxy-5-carboxycyclopentanecarboxylic acid 1,5-dialkyl ester, acctals or ketals with methanesulfonyl chloride. Representative compounds, thus produced, include:

- α-ethyl-2-(1-hydroxypropyl)-3,4-dihydroxy-5-carboxycyclopentanecarboxylic acid 1,5-dieethyl ester, 2-methanesulfonate, acetoinide
- α-propyl-2-(1-hydroxybutyl)-3,4-dihydroxy-5-carboxycyclopentanecarboxylic acid 1-ethyl-5-propyl ester, 2-methanesulfonate, acetoinide
- α-buty1-2-(1-hydroxypentyl)-3,4-dihydroxy-5-carboxycyclopentanecarboxylic acid 2-methyl-5-ethyl ester, 2-methanesulfonate, acetoinide
- α-methyl-2-(1-hydroxyethyl)-3,4-dihydroxy-5-carboxycyclopentanecarboxylic acid 1-butyl-5-methyl ester, 2-methanesulfonate, benzaldehyde acetal
- 2-(1-hydroxyethyl)-3,4-dihydroxy-5-carboxycyclopentanecarboxylic acid 1-propyl-4-ethyl ester, 2-methanesulfonate, diethyl ketone ketal
- α-methyl-2-(1-hydroxyethenyl)-3,4-dihydroxy-5-carboxycyclopentanecarboxylic acid 1-heptyl-5-propyl ester, 2-methanesulfonate, methyl ethyl ketone ketal
- α-ethyl-2-(1-hydroxyethyl)-3,4-dihydroxy-5-carboxycyclopentanecarboxylic acid 1-octyl-5-butyl ester, 2-methanesulfonate, formaldehyde acetal

2-(1-hydroxyethyl)-3,4-dihydroxy-5-carboxycyclopentanecarboxylic acid 1-propyl-5-ethyl ester, 2-methanesulfonate, acetoinide

EXAMPLE 23

2-(1-hydroxyethyl)-3,4-dihydroxy-5-carboxycyclopentanecarboxylic acid 1,5-dimethyl ester, 2-methanesulfonate

A 340 mg. sample of 2-(1-hydroxyethyl)-3,4-dihydroxy-5-carboxycyclopentanecarboxylic acid 1,5-dimethyl ester, 2-methanesulfonate, acetoinide was dissolved in 5 ml. of 60% formic acid-40% water (by volume) and allowed to stand at 25° C. for 2½ hours. The reaction mixture was then evaporated to dryness at 25° C. in vacuo. The residue was dissolved in water and the solution was freeze-dried, leaving 271 mg. of oily 2-(1-hydroxyethyl)-3,4-dihydroxy-5-carboxycyclopentanecarboxylic acid 1,5-dimethyl ester, 2-methanesulfonate which was suitable for the next step.

EXAMPLE 24

α-Methyl-2-(1-hydroxyethyl)-3,4-dihydroxy-5-carboxycyclopentanecarboxylic acid 1,5-dimethyl ester, 2-methanesulfonate

In the manner given in Example 23, α-methyl-2-(1-hydroxyethyl)-3,4-dihydroxy-5-carboxycyclopentanecarboxylic acid 1,5-dimethyl ester, 2-methanesulfonate, acetoinide was hydrolyzed with a mixture of formic acid and water to give α-methyl-2-(1-hydroxyethyl)-3,4-dihydroxy-5-carboxycyclopentanecarboxylic acid 1,5-dimethyl ester, 2-methanesulfonate.

In the same manner given in Example 23, other 2-(1-hydroxyalkyl)-3,4-dihydroxy-5-carboxycyclopentanecarboxylic acid 1,5-alkyl ester, 2-methanesulfonates can be prepared from the corresponding acetals or ketals by hydrolysis with formic acid and water. Representative compounds, thus obtained, include:

- α-ethyl-2-(1-hydroxypropyl)-3,4-dihydroxy-5-carboxycyclopentanecarboxylic acid 1,5-dieethyl ester, 2-methanesulfonate, acetoinide
- α-propyl-2-(1-hydroxybutyl)-3,4-dihydroxy-5-carboxycyclopentanecarboxylic acid 1-ethyl-5-propyl ester, 2-methanesulfonate, acetoinide
- α-buty1-2-(1-hydroxypentyl)-3,4-dihydroxy-5-carboxycyclopentanecarboxylic acid 2-methyl-5-ethyl ester, 2-methanesulfonate, acetoinide
- α-methyl-2-(1-hydroxyethyl)-3,4-dihydroxy-5-carboxycyclopentanecarboxylic acid 1-butyl-5-methyl ester, 2-methanesulfonate, benzaldehyde acetal
- 2-(1-hydroxyethyl)-3,4-dihydroxy-5-carboxycyclopentanecarboxylic acid 1-propyl-4-ethyl ester, 2-methanesulfonate, diethyl ketone ketal
- α-methyl-2-(1-hydroxyethenyl)-3,4-dihydroxy-5-carboxycyclopentanecarboxylic acid 1-heptyl-5-propyl ester, 2-methanesulfonate, methyl ethyl ketone ketal
- α-ethyl-2-(1-hydroxyethyl)-3,4-dihydroxy-5-carboxycyclopentanecarboxylic acid 1-octyl-5-butyl ester, 2-methanesulfonate, formaldehyde acetal

2-(1-hydroxyethyl)-3,4-dihydroxy-5-carboxycyclopentanecarboxylic acid 1-propyl-5-ethyl ester, 2-methanesulfonate, acetoinide

α-ethyl-2-(1-hydroxypropyl)-3,4-dihydroxy-5-carboxycyclopentanecarboxylic acid 1,5-dieethyl ester, 2-methanesulfonate, acetoinide

α-propyl-2-(1-hydroxybutyl)-3,4-dihydroxy-5-carboxycyclopentanecarboxylic acid 1-ethyl-5-propyl ester, 2-methanesulfonate, acetoinide

α-buty1-2-(1-hydroxypentyl)-3,4-dihydroxy-5-carboxycyclopentanecarboxylic acid 2-methyl-5-ethyl ester, 2-methanesulfonate, acetoinide

α-methyl-2-(1-hydroxyethyl)-3,4-dihydroxy-5-carboxycyclopentanecarboxylic acid 1-butyl-5-methyl ester, 2-methanesulfonate, acetoinide

2-(1-hydroxyethyl)-3,4-dihydroxy-5-carboxycyclopentanecarboxylic acid 1-propyl-5-ethyl ester, 2-methanesulfonate, acetoinide

α-ethyl-2-(1-hydroxypropyl)-3,4-dihydroxy-5-carboxycyclopentanecarboxylic acid 1,5-dieethyl ester, 2-methanesulfonate, acetoinide
acid 1,5-dimethyl ester, 2-methanesulfonate was oxidized with aqueous sodium periodate to give α-methyl-2-hydroxy-3-(1-hydroxyethyl)-5-carboxy-3,4-dihydro-2H-pyran-4-acetic acid 4,5-dimethyl ester, 3-methanesulfonate.

In the same manner given in Example 25, other 2-hydroxy-3-(1-hydroxyalkyl)-5-carboxy-3,4-dihydro-2H-pyran-4-acetic acid 4,5-dialkyl esters, 3-methanesulfonates can be prepared from the corresponding glycols (XII) by oxidation with an aqueous periodate salt. Representative compounds thus obtained include:

α-ethyl-2-hydroxy-3-(1-hydroxypropyl)-5-carboxy-3,4-dihydro-2H-pyran-4-acetic acid 4,5-dimethyl ester, 3-methanesulfonate,

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2-hydroxy-3-(1-hydroxybutyl)-5-carboxy-3,4-dihydro-2H-pyran-4-acetic acid 4-ethyl-5-propyl ester, 3-methanesulfonate,

α-butyl-2-hydroxy-3-(1-hydroxypropyl)-5-carboxy-3,4-dihydro-2H-pyran-4-acetic acid 4-ethyl-5-propyl ester, 3-methanesulfonate,

α-buty1-2-hydroxy-3-(1-hydroxypropyl)-5-carboxy-3,4-dihydro-2H-pyran-4-acetic acid 4-butyl-5-methyl ester, 3-methanesulfonate,

2-hydroxy-3-(1-hydroxyethyl)-5-carboxy-3,4-dihydro-2H-pyran-4-acetic acid 4-propyl-5-ethyl ester, 3-methanesulfonate,

2-hydroxy-3-(1-hydroxypropyl)-5-carboxy-3,4-dihydro-2H-pyran-4-acetic acid 4-propyl-5-ethyl ester, 3-methanesulfonate,

A 177 mg. (0.5 millimole) sample of 2-(1-hydroxyethyl)-3,4-dihydroxy-5-carboxy-3,4-dihydro-2H-pyran-4-acetic acid 1,5-dimethyl ester, 2-methanesulfonate was treated with 50 m. of water containing 214 mg. (1.0 millimole) of sodium periodate. The pH of the reaction mixture was adjusted to 6. After stirring 45 minutes, the reaction mixture was extracted 3 times with methylene chloride. The combined methylene chloride solutions were dried over anhydrous sodium sulfate. Distillation of the methylene chloride in vacuo left 160 mg. of oil. Chromatography on 30 g. of silica gel, eluting with acetone benzene (15:85 by volume) gave three compounds. The third compound eluted, consisting of 79 mg., was found to be the desired 2-hydroxy-3-(1-hydroxyethyl)-5-carboxy-3,4-dihydro-2H-pyran-4-acetic acid 4,5-dimethyl ester, 2-methanesulfonate by NMR, IR and UV spectroscopy. The material crystallized on standing.

The material was prepared for analysis by recrystallization from benzene, 30 mg. of colorless crystals of melting point 107-111° C.

Analytical.—Caled. for C14H20O8: C, 44.31; H, .72; S, 9.10. Found (percent): C, 44.23; H, 6.23; S, 9.21.

UV max (95% C14H8O2): 234 m (ε 12,200).

NMR spectrum (CDCl3): 1.57 (3H, d, J = 6 cps., 2.1-3.1 (m), 3.08 (s), 3.68 (3H, s), 3.73 (3H, s), 4.2-8 (2H, m), 5.6-5.8 (1H, m), 7.54 (1H, s).

Example 26

a - Methyl-2-hydroxy-3-(1-hydroxyethyl)-5-carboxy-3,4-dihydro-2H-pyran-4-acetic acid 4,5-dimethyl ester, 3-methanesulfonate

In the manner given in Example 25, α-methyl-2-(1-hydroxyethyl)-3,4-dihydroxy-5-carboxycyclopentaneacetic 75
ester, 3-methanesulfonate was dissolved in 5 ml of pyridine and 3 ml of water and the solution heated on a steam bath for 15 minutes. The reaction mixture was poured into methylene chloride and the methylene chloride layer extracted successively with 1N hydrochloric acid, 5% aqueous sodium bicarbonate and water. The methylene chloride solution was dried over anhydrous sodium sulfate and distilled in vacuo, leaving 356 mg. of oil which crystallized on standing. Recrystallization from benzene-Skellysolve B hexanes gave 73 mg. of colorless prisms of methyl enolate; melting point 93-98°C. This racemic material differs from the purified natural material only in being crystalline; all other physical properties such as IR, UV, and NMR spectrum are identical.

In the same manner given in Example 27, other enolic acid alkyl esters and analogues of Formula XIV can be prepared by heating a 2,4,6-triaryl-3(1-hydroxy-alkyl) -5 - carboxy-3,4-dihydro-2H-pyran-4-acetic acid 4,5-diarylester, 3-methanesulfonate (XIII). Representative compounds, thus obtained, include:

1. 2,3-dimethyl-3-formyl-5-carboxy-3,4-dihydro-2H-pyran-4-acetic acid 4,5-dimethyl ester,
2. 2-butyl-3-formyl-5-carboxy-3,4-dihydro-2H-pyran-4-acetic acid 4,5-diethyl ester,
3. 2-propyl-2-methyl-3-formyl-5-carboxy-3,4-dihydro-2H-pyran-4-acetic acid 4-ethyl-5-propyl ester,
4. 2-ethyl-3-formyl-5-carboxy-3,4-dihydro-2H-pyran-4-acetic acid 4-methyl-5-ethyl ester,
5. 2,3-dimethyl-3-formyl-5-carboxy-3,4-dihydro-2H-pyran-4-acetic acid 4-ethyl-5-propyl ester,
6. 2-propyl-2-methyl-3-formyl-5-carboxy-3,4-dihydro-2H-pyran-4-acetic acid 4-propyl-5-ethyl ester,
7. 2-isopropyl-3-formyl-5-carboxy-3,4-dihydro-2H-pyran-4-acetic acid 4-heptyl-5-propyl ester,
8. 2-ethyl-3-formyl-5-carboxy-3,4-dihydro-2H-pyran-4-acetic acid 4-octyl-5-butyl ester,
9. 2-methyl-3-formyl-5-carboxy-3,4-dihydro-2H-pyran-4-acetic acid 4-isopropyl-5-methyl ester,
10. 2-isopropyl-2-methyl-3-formyl-5-carboxy-3,4-dihydro-2H-pyran-4-acetic acid 4-isobutyl-5-ethyl ester,
11. 2-butyl-2-methyl-3-formyl-5-carboxy-3,4-dihydro-2H-pyran-4-acetic acid 4-pentyl-5-butyl ester,
12. 2-ethyl-2-methyl-3-formyl-5-carboxy-3,4-dihydro-2H-pyran-4-acetic acid 4-hexyl-5-propyl ester,
13. 2-propyl-2-methyl-3-formyl-5-carboxy-3,4-dihydro-2H-pyran-4-acetic acid 4-octyl-5-propyl ester,
14. 2-isopropyl-2-methyl-3-formyl-5-carboxy-3,4-dihydro-2H-pyran-4-acetic acid 4-pentyl-5-methyl ester,
15. 2-methyl-3-formyl-5-carboxy-3,4-dihydro-2H-pyran-4-acetic acid 4,5-dibutyl ester,

and the like.

**Example 28**

Elenolic acid and its calcium salt

A 5.0 g. quantity of methyl enolate was suspended in 50 ml of 0.1 M sulfuric acid and the mixture was heated on a steam bath for 7½ hours. After cooling, saturated aqueous barium hydroxide was added until precipitation of barium sulfate ceased. The mixture was then filtered through a filter aid and the filtrate was freeze-dried. The residue was purified by partition chromatography, using diatomaceous earth as a support and a system consisting of toluene-Skellysolve B hexanes-acetic acid-water (6:4:5:5 by volume). The first peak eluted contained 1.58 g. of material and was found to be methyl enolate by NMR spectroscopy. The second peak was found to contain mainly enolic acid by NMR spectroscopy.

The residue from the evaporation of the second peak fraction was dissolved in water and the solution was stirred with excess calcium carbonate for 4 hours. The mixture was then filtered and the filtrate was freeze-dried, leaving 1.94 g. of product. The NMR showed the material to be reasonably pure calcium enolate.

In the manner given in Example 28, enolic acid analogs of Formula XV are obtained by selectively hydrolysing 2-alkyl-3-formyl-5-carboxy-3,4-dihydro-2H-pyran-4-acetic acid 4,5-diarylester with a dilute mineral acid such as 0.1 M aqueous sulfuric acid.

Representative compounds, thus obtained, include:

1. 2,3-dimethyl-3-formyl-5-carboxy-3,4-dihydro-2H-pyran-4-acetic acid 5-methyl ester,
2. 2-butyl-3-formyl-5-carboxy-3,4-dihydro-2H-pyran-4-acetic acid 5-ethyl ester,
3. 2-propyl-2-methyl-3-formyl-5-carboxy-3,4-dihydro-2H-pyran-4-acetic acid 5-propyl ester,
4. 2-ethyl-3-formyl-5-carboxy-3,4-dihydro-2H-pyran-4-acetic acid 5-ethyl ester,
5. 2-isopropyl-3-formyl-5-carboxy-3,4-dihydro-2H-pyran-4-acetic acid 5-propyl ester,
6. 2-isopropyl-2-methyl-3-formyl-5-carboxy-3,4-dihydro-2H-pyran-4-acetic acid 5-propyl ester,
7. 2-butyl-2-methyl-3-formyl-5-carboxy-3,4-dihydro-2H-pyran-4-acetic acid 5-propyl ester,
8. 2-ethyl-2-methyl-3-formyl-5-carboxy-3,4-dihydro-2H-pyran-4-acetic acid 5-propyl ester,
9. 2-propyl-2-methyl-3-formyl-5-carboxy-3,4-dihydro-2H-pyran-4-acetic acid 5-propyl ester,
10. 2-isopropyl-3-formyl-5-carboxy-3,4-dihydro-2H-pyran-4-acetic acid 5-propyl ester,
11. 2-propyl-2-methyl-3-formyl-5-carboxy-3,4-dihydro-2H-pyran-4-acetic acid 5-propyl ester,
12. 2-ethyl-2-methyl-3-formyl-5-carboxy-3,4-dihydro-2H-pyran-4-acetic acid 5-propyl ester,
13. 2-propyl-2-methyl-3-formyl-5-carboxy-3,4-dihydro-2H-pyran-4-acetic acid 5-propyl ester,
14. 2-ethyl-2-methyl-3-formyl-5-carboxy-3,4-dihydro-2H-pyran-4-acetic acid 5-propyl ester,
15. 2-ethyl-2-methyl-3-formyl-5-carboxy-3,4-dihydro-2H-pyran-4-acetic acid 5-propyl ester,
16. 2-ethyl-2-methyl-3-formyl-5-carboxy-3,4-dihydro-2H-pyran-4-acetic acid 5-propyl ester,
17. 2-ethyl-2-methyl-3-formyl-5-carboxy-3,4-dihydro-2H-pyran-4-acetic acid 5-propyl ester,
18. 2-ethyl-2-methyl-3-formyl-5-carboxy-3,4-dihydro-2H-pyran-4-acetic acid 5-propyl ester,
19. 2-ethyl-2-methyl-3-formyl-5-carboxy-3,4-dihydro-2H-pyran-4-acetic acid 5-propyl ester,
20. 2-ethyl-2-methyl-3-formyl-5-carboxy-3,4-dihydro-2H-pyran-4-acetic acid 5-propyl ester,

and the like.

In a similar manner described for enolic, demethyl-elenolic acid can be prepared which has likewise antiviral activity. For this purpose maleic anhydride is substituted for the citraconic anhydride in Example 3. Carrying the reaction in the reaction with X where X is like manner for X, a compound of Formula XVla is obtained in which R1 is hydrogen.

I claim:

1. A compound of the formula:
3. A compound of the formula:

\[
\begin{align*}
&\text{COOR} \\
&\text{R}_1-\text{CH} \\
&\text{H} \\
&\text{COOH} \\
&\text{COO}\text{H}
\end{align*}
\]

wherein \( R \) is alkyl of 1 to 8 carbon atoms, inclusive where-
in \( R_1 \) is alkyl of 1 to 4 carbon atoms, inclusive, and where-
in \( R_2 \) is selected from the group consisting of hydrogen and alkyl of 1 to 4 carbon atoms, inclusive.

4. A compound according to claim 3 wherein \( R \) and \( R_1 \) are methyl and wherein \( R_2 \) is hydrogen, so that the com-
pound is methyl 2,3-dicarboxy-2-methyl-5-norbornene-7-acetate.

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